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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/998,923      | 12/03/2001  | Laura P. Hale        | 1579-628            | 4251             |

7590 07/23/2004

NIXON & VANDERHYE P.C.  
1100 North Glebe Road, 8th Floor  
Arlington, VA 22201

EXAMINER

UNGAR, SUSAN NMN

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|          | 1642         |

DATE MAILED: 07/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

*SLH*

### Office Action Summary

|                 |              |  |
|-----------------|--------------|--|
| Application No. | Applicant(s) |  |
| 09/998,923      | HALE ET AL.  |  |
| Examiner        | Art Unit     |  |
| Susan Ungar     | 1642         |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on June 2, 2004.  
2a) This action is FINAL. 2b) This action is non-final.  
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-19 is/are pending in the application.  
4a) Of the above claim(s) 8-19 is/are withdrawn from consideration.  
5) Claim(s) \_\_\_\_\_ is/are allowed.  
6) Claim(s) 1-7 is/are rejected.  
7) Claim(s) \_\_\_\_\_ is/are objected to.  
8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) All b) Some \* c) None of:  
1. Certified copies of the priority documents have been received.  
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date August 14, 2002.

4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.  
5) Notice of Informal Patent Application (PTO-152)  
6) Other: \_\_\_\_\_.

1. The Election filed June 2, 2004 in response to the Office Action of January 2, 2004 is acknowledged and has been entered. Claims 1-19 are pending in the application and Claims 8-19 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-7, species plasma, species immunoassay are currently under prosecution.
2. It is noted that upon review and reconsideration it has been found that it was known in the art since the 1960's that ZAG is present in all bodily liquids and therefore the requirement for an election of species drawn to bodily liquid has been withdrawn as each of the claimed body liquids is obvious, one over the other.
3. Applicant's election with traverse of Group 1, claims 1-7, species serum (which species restriction requirement is now withdrawn) and immunoassay is acknowledged. The traversal is on the ground(s) that the subject matter of Groups 2-8 and Group 1 are classed and subclassed identically, thus it is believed that no undue burden would be placed on the Examiner if all of Groups 1-8 were to be considered in the same application. The argument has been considered but have not been found persuasive because classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

***Specification***

4. The specification on page 1 should be amended to reflect the status of the parent application.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

6. Claims 1-7 are rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the claimed invention.

The claims are drawn to a method for diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a control sample wherein an elevated level of ZAG in the biological sample from said test mammal relative to said control is indicative of the presence of a tumor.

The specification teaches that ZAG concentrations can be used to diagnose a variety of tumor types including prostate, breast, colon, squamous cell and pancreatic cancers. In particular, the specification teaches that high levels of ZAG are present in prostate cancer serum, whereas lower levels are present in BPH serum or the serum of normal controls (see p. 9). It appears also that patients with enlarged normal prostate present with high

levels of ZAG (p. 10, lines 105). Todorov et al, Cancer Res. 1998, 58:2353-2358 (IDS item) quantitated ZAG production by MAC16 colon adenocarcinoma tumors wherein MAC16 produced large quantities of ZAG when compared to normal controls (p. 3, lines 1-17).

One cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known in the art that ZAG overexpression is associated with cachexia , a physical decrease in carcass lipid seen in a variety of chronic and severe diseases. These diseases include as cancer, Aids, sleeping sickness, schistsomiasis and tuberculosis (Kennedy et al, 7<sup>th</sup> International Symposium on Schistosomiasis, Abstract). Thus, it would appear that it is not possible to diagnose a specific disease based on ZAG concentrations. It is noted that ZAG is a soluble protein found in all body fluids. It is secreted by a variety of normal and malignant epithelial cells, thus its appearance in serum is an inherent property of the protein and serum concentrations of the protein would be expected to be sensitive to overexpression of the protein. As taught by Poortmans et al (J. Lab. Clin. Med., 1968, 71:807-811) ZAG is found in urine, saliva and sweat (p. 809). Poortmans et al further teaches that preferential urinary excretion of plasma proteins with small molecular sizes is a well known phenomenon and that saliva and sweat secretions also contain a high level of ZAG (p. 810). Further, ZAG over-production from tumors has been associated with lipolysis and cachexia in advanced cancers (see Wang et al, 3<sup>rd</sup> Annual Western Canadian Structural Biology Workshop, Frontiers in Structural Biology, November 20-23, 2003, Banff, Alberta, Canada, see Abstract). During cachexia, ZAG production is increased 10-fold (see World Health News, November 7, 2003, abstract, Obesity Pill Near). Interestingly,

Todorov et al, *Supra*, specifically teach that cancer patients with weight loss showed urinary excretion of ZAG while cancer patients without weight loss or normal subjects did not (see abstract). Given the above, it is clear that cachexia is associated with the overexpression of ZAG and that the biological fluid increases of ZAG concentration found in cancer patients is not associated with the cancer *per se*, but rather is associated with the cachexia, which is a concomitant characteristic presented by some of the patients suffering from a variety of chronic and severe diseases. Given the above, it cannot be predicted that an increase in ZAG in plasma or any other biological fluid would be indicative of a tumor, rather than indicative of AIDS, sleeping sickness, schistosomiasis or tuberculosis or any other diseases associated with cachexia. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention could be used with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. If Applicant were able to overcome the rejection under 35 USC 112, first paragraph above, Claims 1-7 would still be rejected under 35 USC 112, first paragraph because the specification, while enabling for a method of diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a biological sample from a matched sample wherein said sample is from the same population, the biological sample is from the same tissue and analyzed using the same technique, wherein an elevated level of ZAG in

the biological sample from the test mammal relative to the control is indicative of the presence of a tumor, does not reasonably provide enablement for a method of diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a biological sample from a control, non-tumor bearing mammal, wherein an elevated level of ZAG in the biological sample from the test mammal relative to the control is indicative of the presence of a tumor. The invention was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the claimed invention.

The claims are drawn to a method of diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a biological sample from a control, non-tumor bearing mammal, wherein an elevated level of ZAG in the biological sample from the test mammal relative to the control is indicative of the presence of a tumor. This means that the control can be from any species comprising any tissue. The specification teaches that the concentration of ZAG in normal human plasma or serum has been variously reported as between 25-140 ug/ml in different populations using various analytic techniques and may increase with age (p. 2, lines 10-12).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification clearly teaches the wide variation of normal serum/plasma levels of ZAG. Given the wide variation of normal levels, it is not clear how, in the absence of using the same population to supply the control sample and the same technique to assay both samples, an

appropriate base-line can be established so that it is possible to determine whether or not the level of ZAG in the test sample is in fact elevated. Further, as drawn to using the same tissue, Poortman et al, (J. Lab. Clin. Med., 1968, 71:807-811) specifically teaches that the level of ZAG in normal serum (14 mg/100ml) and cerebrospinal fluid is low but that it is high in urine, saliva and sweat as compared to total protein content. Given the clear differences in ZAG concentration in various biological tissues, it cannot be predicted that a determination of the presence of a tumor can be made using a control that is not from the same tissue as the test sample. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the methods as claimed can be used with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. If Applicant were able to overcome the rejections under 35 USC 112, first paragraph above, Claims 6-7 would still be rejected under 35 USC 112, first paragraph because the specification, while enabling for a method of diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a biological sample from control, wherein an elevated level of ZAG in the biological sample from the test mammal relative to the control is indicative of the presence of a tumor, does not reasonably provide enablement for a method of diagnosing prostate cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a biological sample from

a control, non-tumor bearing mammal, wherein an elevated level of ZAG in the biological sample from the test mammal relative to the control is indicative of the presence of a prostate tumor. The invention was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to use the claimed invention.

The claims are drawn to a method of diagnosing prostate cancer. The specification teaches that ZAG concentrations can be used to diagnose a variety of tumor types including prostate, breast, colon, squamous cell and pancreatic cancers. In particular, the specification teaches that high levels of ZAG are present in prostate cancer serum, whereas lower levels are present in BPH serum or the serum of normal controls (see p. 9). It appears also that patients with enlarged normal prostate present with high levels of ZAG (p. 10, lines 105). Todorov et al, Cancer Res. 1998, 58:2353-2358 (IDS item) quantitated ZAG production by MAC16 colon adenocarcinoma tumors wherein MAC16 produced large quantities of ZAG when compared to normal controls (p. 3, lines 1-17).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification provides neither guidance on or exemplification on how to distinguish the source of elevated ZAG concentrations in any biological fluid, that is, whether the source is a prostate, breast, colon, squamous cell or pancreatic cancer. In particular, Todorov specifically teach that patients with pancreatic cancer, chorangiocarcinoma, pancreatic cancer, ovarian cancer, hepatoma, perampullary cancer overexpress ZAG compared to normal control (p. 2355, Table 1). Further, Lopez-Otin et al, (Endocrine Reviews, 198, 19:365-396,

IDS item) specifically teaches that ZAG is produced by both benign and malignant prostatic tumors (see Table 2, p. 375). In addition, it was found that intraprostatic analysis demonstrated that the values of ZAG were strikingly higher in BPH than in adenocarcinomatous prostates, reflecting the dedifferentiation of cancerous prostates with the loss of secretory activity. These results agree with other studies (p. 337, col 2). It would be expected that these results would be reflected in biological liquids. Given that ZAG is expressed by both BPH and prostate tumor cells, given that the expression of ZAG is less in tumor cells as compared to BPH, given that ZAG is a secreted protein and the reference specifically teaches that there is a loss of secretory activity, it cannot be predicted that the invention will function as claimed as the specification provides no information as to how to differentiate between BPH and prostate cancer or which elevated level is the one that would be predictable for prostate cancer. In particular since it was known in the art that both BPH and prostate tumor cells secrete ZAG. The specification provides insufficient guidance with regard to this issue and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that how the methods as claimed can be used with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

9. Claims 1-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite in the recitation, in claim 1, of the term “tumor”. The claims are confusing because the preamble of the claim is

drawn to a method of diagnosing cancer and yet the body of the claim is drawn to a “tumor” which is known in the art to be a term used to define both a malignant tumor, or cancer, and a benign tumor. The rejection can be obviated by amending the claims, for example, to recite “malignant tumor” or by deleting the term “tumor” and substituting the term “cancer”.

***Claim Rejections - 35 USC §102***

10. Claims 1, 4 and 5 are rejected under 35 USC 102(b) as being anticipated by Bundred et al, (Histopathology, 1987, 11:603-610, IDS item).

The claims are drawn to a method of diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a biological sample from a control, non-tumor bearing mammal, wherein an elevated level of ZAG in the biological sample from said test mammal relative to said control is indicative of the presence of a tumor (claim 1), wherein the level of ZAG is assayed using an immunoassay (claim 4), wherein the assay is an antigen capture assay (claim 5).

Bundred et al teaches a method of identifying/diagnosing breast cancer in a patient comprising assaying for ZAG using an immunoassay, an antigen capture assay (p. 605) wherein a progression was apparent from normal to hyperplastic breast in the number of cells reacting with anti-ZAG antibody, wherein it was found that ZAG was demonstrated in 16 of 33 invasive carcinomas (see abstract), wherein only occasional focal staining of a few acinar and intralobular ductal epithelial cells was found in normal breast tissue (p. 606).

11. Claims 1-3 are rejected under 35 USC 102(b) as being anticipated by Lopez-Otin et al, (Endocrine Reviews, 198, 19:365-396, IDS item).

The claims are drawn to a method of diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a biological sample from a control, non-tumor bearing mammal, wherein an elevated level of ZAG in the biological sample from said test mammal relative to said control is indicative of the presence of a tumor (claim 1), wherein the sample is a liquid sample (claim 2), wherein the sample is a nipple aspirate sample (claim 3).

Lopez-Otin et al specifically teach that a significant percentage of mammary tumors produce and secrete appreciable amounts of ZAG, wherein the higher levels of ZAG were found in histopathologically well-differentiated tumors than in moderately or poorly differentiated tumors suggesting that this protein may be a marker of tumors with a high degree of differentiation, low metastatic potential and therefore with favorable clinical outcome.

Although the reference does not specifically state that the level of ZAG is elevated relative to a control, the statement drawn to “appreciable amounts of ZAG” appears to infer that there was a comparison made with a normal control. Further, although the reference does not specifically state that the secretions assayed were nipple aspirate samples, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is

different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 872-9306.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar  
Primary Patent Examiner  
July 21, 2004